## REMARKS

The specification has been amended to insert a statement that the present application is a divisional of U.S. Application Serial No. 09/470,667, filed December 22, 1999, now U.S. Patent No. 6,730,503, which is a divisional of U.S. Application Serial No. 08/934,506, filed September 19, 1997, now abandoned.

Claim 1 has been amended to recite "[a]n enzyme having alcohol and aldehyde dehydrogenase activity comprising an isolated polypeptide encoded by a DNA molecule according to SEQ ID NO: 4 or encoded by a DNA sequence, which hybridizes under standard conditions with said DNA molecule." Support for this amendment is found in original claim 1 and in the specification at, for example, page 4, lines 16-23 and page 16, lines 1-15. *See In re Gardner*, 177 USPQ 396, 397 (CCPA 1973) and MPEP §§ 608.01 (o) and (l).

Claim 2 has been amended to recite "[a]n enzyme of claim 1 having alcohol and aldehyde dehydrogenase activity, wherein the isolated polypeptide is a chimeric polypeptide including a combination of at least two amino acid sequences each of said sequences being selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 8, and amino acid sequences encoded by DNA sequences hybridizing under standard conditions with DNA molecules according to SEQ ID: 4 or 1." Support for this amendment is found in original claim 2 and in the specification at, for example, page 4, lines 8-23 and page 16, lines 1-15. (*Id.*).

Claim 9 has been amended to recite "[a]n isolated enzyme produced by expression of vector pSSB103R." Support for this amendment is found in original

claims 8 and 9 and in the specification at, for example, page 10, lines 11-16 and page 36, lines 7-15. (*Id.*).

Claim 25 has been amended to recite "[a] process for producing 2-keto-L-gulonic acid which comprises: (a) incubating a reaction mixture containing a substrate selected from the group consisting of D-sorbitol and L-sorbose, and an enzyme according to claim 1, and (b) converting the substrate to 2-keto-L-gulonic acid." Support for this amendment is found in original claims 1 and 25 and in the specification at, for example, page 4, lines 16-23 and page 16, lines 1-15. (*Id.*).

Claim 30 has been amended to recite "[a]n isolated enzyme having alcohol and aldehyde dehydrogenase activity encoded by a recombinant expression vector comprising a DNA sequence of SEQ ID NO: 4 or a DNA sequence which hybridizes under standard conditions with said DNA molecule, wherein the DNA sequence is functionally linked to one or more genetic control sequences and is capable of expression of an enzyme including at least one recombinant polypeptide having alcohol and aldehyde dehydrogenase activity." Support for this amendment is found in original claim 30 and in the specification at, for example, page 4, lines 16-23 and page 16, lines 1-15. (*Id.*).

Claim 31 has been amended to recite "[a]n isolated enzyme having alcohol and aldehyde dehydrogenase activity encoded by a recombinant expression vector comprising a DNA sequence of SEQ ID NO: 4 or a DNA sequence which hybridizes under standard conditions with said DNA molecule." Support for this amendment is found in original claim 31 and in the specification at, for example, page 4, lines 16-23 and page 16, lines 1-15. (*Id.*).

It is submitted that no new matter has been introduced by the foregoing amendments.

**Priority:**

The Examiner apparently objected to Applicants' claim to priority. In making the objection, the Examiner asserted that the prior claim to benefit present in the March 17, 2004 Response was incomplete in its failure to note that the '667 application was allowed. (Paper No. 100705 at 2).

With a view toward furthering prosecution, the specification has been amended to recite that the present application "is a divisional of U.S. Application Serial No. 09/470,667, filed December 22, 1999, now U.S. Patent No. 6,730,503, which is a divisional of U.S. Application Serial No. 08/934,506, filed September 19, 1997, now abandoned." In view of the foregoing, it is respectfully submitted that the claim to benefit has been perfected.

**Objection:**

The Examiner objected to claim 9 for use of the language "[a]n enzyme produced by vector." (*Id.* at 3). The Examiner suggested alternative language to overcome the objection, namely: "an isolated enzyme produced by an expression of vector." (*Id.*).

With a view towards furthering prosecution, claim 9 has been amended as suggested by the Examiner to recite "[a]n isolated enzyme produced by expression of vector pSSB103R." In view of the foregoing amendment, the objection of claim 9 is rendered moot. Accordingly, withdrawal of the objection is respectfully requested.

**35 U.S.C. § 101 Rejection:**

Claims 1-3, 9, and 29-31 have been rejected under 35 U.S.C. § 101. (Paper No. 100705 at 3).

In making the rejection, the Examiner asserted that "the claimed invention is directed to non-statutory subject matter" and that "[i]n the absence of the hand of man, naturally occurring proteins and/or nucleic acids are considered non-statutory subject matter." (*Id.*). The Examiner suggested language to overcome the rejection, namely: "An isolated and purified protein or nucleic acid." (*Id.*).

With a view towards furthering prosecution, claims 1-3, 9, and 29-31 have been amended (or depend from a claim that has been amended) as suggested by the Examiner. In view of the foregoing, the rejection of claims 1-3, 9, and 29-31 is rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

**35 U.S.C. § 112, First Paragraph, Rejections:**

Claims 1-3, 9, 20-22, 25, 28, and 30-31 have been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. (Paper No. 100705 at 5).

In making the rejection, the Examiner asserted that "the specification ... does not reasonably provide enablement for any amino acid sequence comprising a sequence that has at least 80% identity to SEQ ID NO: 8." (*Id.*). The Examiner acknowledged, however, that the specification is "enabling for the alcohol and aldehyde dehydrogenase of SEQ ID NO: 5, 6, 7 and 8." (*Id.*).

In response to Applicant's remarks submitted May 11, 2005, the Examiner stated "Applicants' argument has been fully considered but is found not persuasive for the following reasons. Table 7 quotes the homology of SEQ ID NO: 5-8 to each other.

This, however, does not provide for structural identification of the enzyme having the AADH activity and being at least 80% homologous to any of SEQ ID NO: 5, 6, 7, 8. As Applicants rightfully emphasize, this is 'a small number of enzymes' and not four genera or any combination of four[ ] genera as broadly claimed. For that reason the invention as claimed is not enabled and imposes undue experimentation on a skilled artisan." (*Id.* at 6).

Initially, we note that it is the Examiner's burden to demonstrate that a specification is not sufficiently enabling. *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971). To carry her burden, the Examiner must identify and clearly articulate the factual bases and supporting evidence that allegedly establish that undue experimentation would be required to carry out the claimed invention. *Id.* at 370.

With a view towards furthering prosecution, claim 1 has been amended to recite "[a]n enzyme having alcohol and aldehyde dehydrogenase activity comprising an isolated polypeptide encoded by a DNA molecule according to SEQ ID NO: 4 or encoded by a DNA sequence, which hybridizes under standard conditions with said DNA molecule." Claim 2 has been amended to recite "[a]n enzyme of claim 1 having alcohol and aldehyde dehydrogenase activity, wherein the isolated polypeptide is a chimeric polypeptide including a combination of at least two amino acid sequences each of said sequences being selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 8, and amino acid sequences encoded by DNA sequences hybridizing under standard conditions with DNA molecules according to SEQ ID: 4 or 1." Claim 25 has been amended to depend from claim 1. And claims 30 and 31 have been amended to recite "[a]n isolated enzyme having alcohol and aldehyde dehydrogenase activity encoded by a recombinant expression vector comprising a DNA sequence of

SEQ ID NO: 4 or a DNA sequence which hybridizes under standard conditions with said DNA molecule."

We note that the phrase "hybridizes under standard conditions" is an art-recognized term that one skilled in the art would understand, even without further guidance from the specification. Nevertheless, the specification as filed provides details as to how this term is to be interpreted, *see, e.g.*, page 16, lines 9-15. For exact details of these hybridization procedures, the specification cites to Sambrook *et al.*, Molecular Cloning (2nd ed.), Cold Spring Harbor Laboratory Press 1989, New York. For the Examiner's convenience, a copy of the relevant passages from the Sambrook textbook is enclosed. (Exhibit 1).

The specification discloses that the nearest homologues of Enzyme B (SEQ ID NO: 8) exhibit a maximum homology of 26-31% with known enzymes (page 34, line 20 to page 35, line 4):

> Homology search of Enzymes A, A', A" and B revealed that Enzymes A, A', A" and B showed rather low homology (26-31% homology through the polypeptides) with several quino-proteins including alcohol dehydrogenase of *Acetobacter aceti* (T. Inoue et al., J. Bacteriol. 171: 3115-3122) or *Acetobacter polyoxogenes* (T. Tamaki et al., B.B.A., 1088: 292-300), and methanol dehydrogenase of *Paracoccus denitrificans* (N. Harms et al., J. Bacteriol., 169: 3966-3975), *Methylobacterium organophilum* (S.M. Machlin et al., J. Bacteriol., 170: 4739-4747), or *Methylobacterium extorquens* (D.J. Anderson et al., Gene 90: 171-176).

One skilled in the art would immediately recognize that the DNA encoding such known enzymes would ***not*** hybridize under "standard conditions" to the DNA encoding SEQ ID NO: 8 (*i.e.*, a DNA according to SEQ ID NO: 4). Thus, such known enzymes would not fall within the scope of the currently claimed subject matter.

Table 7 of the specification details the degree of homology between the AADH (Alcohol/Aldehyde Dehydrogenases) of SEQ ID NO: 8 and three other amino acid sequences having AADH activity, *i.e.*, SEQ ID NOS: 5, 6 and 7, which are disclosed throughout the specification. The results in Table 7 demonstrate that a homology of at least 80% was detected:

Table 7. Homologies of amino acid sequences among AADHs.

| | Enzyme A | Enzyme A' | Enzyme A" | Enzyme B |
|---|---|---|---|---|
| Enzyme A | 100 | _ | _ | _ |
| Enzyme A' | 89 | 100 | _ | _ |
| Enzyme A" | 85 | 86 | 100 | _ |
| Enzyme B | 83 | 82 | 81 | 100 |

(See specification at page 34, lines 15-20). As discussed above, the next highest homology between Enzymes A, A', A", and B to enzymes with known alcohol or methanol dehydrogenase activity was in the range of 26 to 31%. (See Specification at page 34, line 20 to page 35, line 4). Thus, the data in Table 7 clearly provides evidence that the Applicants enabled the full scope of the amended claims by unambiguously identifying enzymes having highly homologous polypeptide sequences and sharing a common function -- AADH activity. Accordingly, it is respectfully submitted that undue experimentation would not be required to carry out the currently claimed invention.

For the reasons set forth above, the enablement rejection should be withdrawn.

Claims 2-3 have also been rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. (Paper No. 100705 at 5).

In making the rejection, the Examiner asserted that claims 2 and 3 "do[ ] not reasonably provide enablement for an enzyme that comprises a combination of at least two amino acids sequences each of said sequences being selected from the group of SEQ ID NO: 8 and SEQ ID NO: 5 and amino acid sequences that are at least 80% identical to SEQ ID NO:8 or SEQ ID NO: 5." (*Id.*). The Examiner, however, acknowledged that claims 2 and 3 are "enabling for the plasmid comprising genes encoding SEQ ID NO: 5 and SEQ ID NO: 8 (plasmids pSSAB201 and pSSBA201)." (*Id.*).

With a view towards furthering prosecution, claims 1 and 2 have been amended. Claim 1 (from which claim 3 depends) has been amended to recite "[a]n enzyme having alcohol and aldehyde dehydrogenase activity comprising an isolated polypeptide encoded by a DNA molecule according to SEQ ID NO: 4 or encoded by a DNA sequence, which hybridizes under standard conditions with said DNA molecule." Claim 2 has been amended to recite "[a]n enzyme of claim 1 having alcohol and aldehyde dehydrogenase activity, wherein the isolated polypeptide is a chimeric polypeptide including a combination of at least two amino acid sequences each of said sequences being selected from the group consisting of SEQ ID NO: 5, SEQ ID NO: 8, and amino acid sequences encoded by DNA sequences hybridizing under standard conditions with DNA molecules according to SEQ ID: 4 or 1."

We note that the construction of the currently claimed chimeric nucleic acid molecules and polypeptides is specifically disclosed in the specification at, for example, Examples 14 and 15 and in Figures 2, 3, 4, 7, and 8. The specification also discloses the enzymatic activity of these constructs (*see, e.g.*, Figure 11). Furthermore, the specification discloses in Tables 11 and 12 comparisons of the substrate

specificities of the claimed enzymes. Thus, the specification clearly enables the full scope of the currently claimed chimeric enzymes (*i.e.*, the chimeric enzymes identified as Enzyme B (*i.e.*, SEQ ID NO: 8) and Enzyme A (*i.e.*, SEQ ID NO: 5) and the chimeric enzymes encoded by DNA sequences hybridizing under standard conditions with DNA molecules according to SEQ ID: 4 or 1).

In addition, the structure of the claimed chimeras can easily be obtained by one skilled in the art from the information disclosed in the specification (*i.e.*, the sequence listing in combination with the Figures and Examples 14 and 15). Thus, the skilled person is not left "without a[ny] further guidance" as asserted by the Examiner. (Paper No. 100705 at 5).

In view of the foregoing, it is respectfully submitted that the rejection has been rendered moot. Accordingly, withdrawal of the rejection is respectfully requested.

For the foregoing reasons, favorable action on the merits, including entry of the amendments, withdrawal of the objections and rejections, and allowance of all the claims, respectfully are requested. If the Examiner has any questions regarding this paper, please contact the undersigned attorney.

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box. 1450 Alexandria, VA 22313-1450, on April 20, 2006.

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